DM

September 1955

Disease-a-Month

Viral Hepatitis

ROBERT E. SHANK

THE YEAR BOOK PUBLISHERS • INC.
CHICAGO

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Robert E. Shank

received his doctorate of medicine from the Washington University School of Medicine and obtained experience and training in internal medicine at Barnes Hospital in St. Louis. He served on the staff of the Hospital of the Rockefeller Institute for Medical Research from 1942 to 1946, and later held appointment as Research Associate in the Division of Nutrition and Physiology of the Public Health Research Institute of the City of New York. Since 1948 he has been Professor of Preventive Medicine and Head of the Department at Washington University. He is Associate Physician of Barnes Hospital and directs the activities of the Hepatic Clinic and the Nutrition Research Laboratory. His chief research interests have been concerned with diseases of the liver, disorders of muscles and problems in nutrition.

VIRAL HEPATITIS is one of the most common and important infectious diseases in the world today. Nearly 50,000 cases were reported in the United States in 1954, the total number being exceeded only by those of measles, scarlet fever and streptococcic sore throat, and pertussis in the listing of Specified Notifiable Diseases (1). However, viral hepatitis, as a disease entity, is important to the physician not only because of the frequency of its occurrence but for other reasons as well. For instance, two forms of the disease are recognized, and in one of these the physician often bears the responsibility of disseminating the agent as he utilizes blood or blood products or improperly sterilized equipment in treating other disorders. In addition, there are problems of diagnosis, particularly early in the course or when the disease occurs without producing icterus. Moreover, specific modes of treatment are not available, and the relatively long period of convalescence is of economic disadvantage to the patient. Finally, while viral hepatitis does produce massive hepatic necrosis and death in rare instances, more frequently the

disease is prolonged and the patient is left with residuals of chronic liver disease and hepatic dysfunction. The purpose of this paper is to review the present knowledge of the disease and to discuss some of the problems presented by it.

ETIOLOGIC AGENTS

It is perhaps surprising that knowledge of the cause and natural history of a disease as prevalent as viral hepatitis remained so limited until recently. Large epidemics of grave military significance during World War II gave impetus to the study of viral hepatitis and added important fundamental considerations to the basic understanding of the disease process and its etiology and control.

Two forms of the disease are recognized. The first, *infectious hepatitis,* occurs endemically and epidemically in most, if not all, areas of the world. It is spread by person-to-person contact and by contamination of food or water supplies. The second form of viral hepatitis, *serum hepatitis,* may not be readily differentiated, in terms of clinical manifestations or pathologic anatomy, from infectious hepatitis. In this form the virus is disseminated by means of blood or by materials or equipment contaminated with blood from individuals who are carriers of the virus. Serum hepatitis is, therefore, induced by the physician in carrying out necessary diagnostic and therapeutic procedures. It is characterized by a remarkably long incubation period. Currently available information warrants the view that two different and unrelated viruses are responsible for the occurrence of infectious hepatitis and serum hepatitis. The infectivity of both viruses seems to be limited to man, since attempts to infect other animal species have thus far proved unsuccessful. This is true despite the fact that spontaneously occurring involvement of the liver by other infections apparently of viral origin have been observed and described in dogs, horses, swine, mice and canaries.

Infectious hepatitis (ih virus).—The agent producing infectious hepatitis passes through filters which retain bacterial organisms and is, therefore, presumed to be a virus. It is relatively resistant to physical and chemical agents, surviving temperatures of 56 C. for more than 30 minutes and remaining viable in water

which has been chlorinated and contains a residual of one part chlorine per million. Recognition of the viral agent and demonstration of its presence in suspected materials has depended entirely on inoculation of human volunteers. By this means, much important information has been provided (2, 3). However, the number of volunteers available for such experiments has necessarily limited the experiments undertaken and the conclusiveness with which many findings are established. The infectivity of serum and fecal filtrates from patients in the preicteric phase or early icteric phase of infectious hepatitis has been clearly established in volunteer subjects. Serum samples produce infection when administered both by parenteral injection and by mouth, and there is no conclusive proof that urine or nasopharyngeal washings are infective. Relatively little information is available which would permit deductions concerning the time of earliest appearance of the virus in blood or feces or the length of the period in which the average patient remains infective. It seems reasonable to assume, however, that viremia occurs in advance of symptoms and that virus is usually present in blood and feces for at least a week, and perhaps for a longer period, after the occurrence of symptoms. The presence of IH virus in blood makes possible the induction of hepatitis by injection of contaminated materials. Indeed, it is likely that some cases of serum hepatitis are, in reality, infection with IH virus. Such an infection produces a disease with a shorter incubation period than is characteristic of serum hepatitis.

The disease induced by IH virus characteristically develops after an incubation period of from 14 to 40 days. In spontaneously occurring infection and in volunteers, infection ordinarily results in the production of some degree of immunity. This fact is attested to by epidemiologic data indicating common occurrence of the disease in early life but low incidence in adulthood. In addition, challenge of volunteers with the virus following convalescence from prior infection has usually failed to produce infection (3). On the other hand, it should be recognized that bona fide instances of reinfection do occur. In military experience about 5% of patients have a history of previously occurring viral hepatitis. Gamma globulin produced from pooled human plasma has been shown to afford passive protection against infectious hepatitis when administered early in

the incubation period of the disease (4, 5) and has provided indirect evidence of an antibody in a significantly great proportion of the donor population. A skin test has been proposed for use in demonstrating immunity to IH virus (6). This utilizes virus propagated in the chick embryo. Unfortunately, transfer of the virus in the chick embryo either is not readily and reproducibly accomplished or has not been wholly proved. Specific immunologic procedures of this type would be of inestimable value in determining the type and nature of infection, if perfected.

SERUM HEPATITIS (SH VIRUS).—Serum hepatitis is also caused by a filterable infectious agent which is relatively resistant to physical and chemical conditions lethal to other organisms, a characteristic contributing greatly to the difficulties in controlling the disease. The virus retains infectivity after heating at 56 C. for one hour and is preserved for long periods at refrigerator temperatures or when frozen. Although it has been observed that the virus remains viable in the desiccated state when stored at room temperature for months, evidence indicates that SH virus in serum fails to withstand prolonged storage at room temperature (7). Ultraviolet irradiation may destroy the agent, but its lethal effect cannot be totally relied upon in the sterilization of blood products (3, 8). Virus in serum is not destroyed by Merthiolate in a concentration of 1:2000, by a mixture of phenol and ether in equal proportions and in 0.5% concentration or by 0.2% tricresol (3). Concentrations of ethyl alcohol ordinarily lethal to bacterial organisms do not kill the SH virus, since the disease has been transmitted by needles and syringes sterilized by washing and storing in solutions of ethyl alcohol.

Parenteral injection of serum containing the SH virus has produced hepatitis in volunteers after an incubation period of 30–160 days, while introduction by the oral route has failed to produce the disease. Similarly, ingestion of filtrates of fecal material and nasopharyngeal washings from patients in the acute stages of serum hepatitis has not caused infection. It should be pointed out, however, that it is perhaps presumptious to conclude that the virus is not present in feces, because there is no definitive evidence that fecal filtrates injected parenterally do not cause infection.

Samples of serum taken as early as 87 days before the occurrence of the first symptoms in volunteers have proved to be icterogenic

(9). Viremia, therefore, occurs early and probably persists throughout the incubation period. Although efforts have been made to demonstrate the virus in the serum of volunteers at intervals after the onset of illness, these have proved singularly unsuccessful. Therefore, it cannot be stated how long viremia persists. Clinical evidence, however, indicates that SH virus may remain in the blood of certain individuals for many months or years. Such a state may occur after clinically manifest disease or in carriers without prior illness. The virus must occur in high titer or in great quantity in certain sera, since injection of as small a quantity as 0.00001–0.0001 ml. of serum has induced infection. Recent observations give evidence that the virus can be transmitted through the placenta to the fetus in utero (10). Neefe suggests that this may be the natural method of propagation of the virus, in contrast to the artificial dissemination through diagnostic and therapeutic efforts of physicians (11).

Observations in volunteers warrant the view that infection with SH virus produces homologous immunity. Challenge of such subjects with icterogenic serum containing SH virus following recovery from serum hepatitis has uniformly failed to result in infection; but IH virus similarly administered may induce hepatitis, demonstrating the lack of heterologous protection. Unlike infectious hepatitis, the gamma globulin fraction of human plasma proteins has not been shown to confer passive immunity against serum hepatitis.

EPIDEMIOLOGY

INFECTIOUS HEPATITIS.—Until recent years, "infectious hepatitis" has been but one of a number of appellations by which this particular disease was designated. Included in older terminology were "catarrhal jaundice," "infective hepatitis" and "epidemic jaundice or hepatitis." Although more adequate description of the etiology and natural history of infectious hepatitis has been a development of the last 15 years, the disease has been prevalent in the Western world for centuries and epidemics have occurred at frequent intervals. The cyclic occurrence of epidemics of variable size and importance is well demonstrated in the data available from Sweden, where hepatitis or jaundice has been reported since 1901

(12). Outbreaks in institutional groups, such as in children's homes, schools and summer camps, have been described frequently. Of singular importance is the common association of large epidemics with military campaigns. Descriptions are available of the occurrence of infectious hepatitis in epidemic proportions in all the military campaigns in which the forces of the United States have engaged, except the Revolutionary War. It is perhaps no exaggeration to state that infectious hepatitis and serum hepatitis, together, represented the most important infectious disease confronting the armed forces during World War II in terms of morbidity and loss of time in convalescence.

The presence of the virus in feces warrants the view that the usual mode of transmission is by the intestinal-oral route. Close personal contacts, as in family groups, schools and military companies, are undoubtedly of first importance in the dissemination of the disease. However, contamination of ingested food or water supplies has been a factor in certain outbreaks. Reports in the literature demonstrate contamination of water, milk and food (13, 14, 15). The necessity for considering the possibility of spread by the respiratory route is indicated because of the demonstrated importance of close personal contact. However, nasopharyngeal washings have not proved infectious in experimental transmission. The presence of virus in the blood early in the disease makes dissemination possible in the hospital or in the physician's office if syringes and needles are not properly sterilized. This fact also indicates a possibility that biting or blood-sucking insects may afford mechanical or biologic means of spread. At this time, however, there is no information incriminating any insect vector.

Infectious hepatitis may occur in any month or season, but the seasonal incidence usually demonstrates an increase in the number of cases in early fall with a peak in early winter, and decreasing incidence through spring and early summer in temperate zones. Although fall and winter peaks of incidence are usual, summer epidemics of the disease are not uncommon.

The age distribution of afflicted persons indicates greatest susceptibility in the earlier years of life, with greatest incidence in the years from 5 to 15 (16). Apparent lower incidence in the first five years of life may be due to more frequent occurrence of infec-

tion without icterus or symptoms. During epidemics it has been noted that the incidence is higher among children of 10–14 years than in the group from 5 to 9. Attack rates in outbreaks in schools may be as high as 30%, and children of the two sexes seem to be equally susceptible. In adults the incidence is similar for men and women, and attack rates in explosive epidemics among military personnel have been as high as 40–50%.

During endemic periods, infectious hepatitis is usually of higher incidence in towns and cities than in rural areas. In epidemics, however, the incidence seems to be uniformly higher in rural groups. This is explained on the basis of lower prevalence in inter-epidemic periods and less highly developed sanitary controls among rural groups, permitting more ready spread of infection. Primary and secondary waves of infection are recognized during epidemics and contact cases occur, usually with incubation periods varying in length from 20 to 40 days.

Host characteristics may be important in determining the course and outcome of infection with the IH virus. There are indications that sex or hormonal factors condition the severity of the disease. In an epidemic in Denmark, mortality from the infection was greatest among women in the postmenopausal period, with case fatality rates as high as 50% in this group (17, 18). The disease also may occur in particularly malignant form in women during the latter half of pregnancy, with death due to acute or subacute hepatic atrophy, a syndrome referred to more commonly in the past as "acute or subacute yellow atrophy" (19). The author has observed similar rapidly progressive and fatal infection in three adolescent girls shortly after the onset of the menarche. Other observations indicate that infectious hepatitis may be associated with high mortality in the first year of life (20).

SERUM HEPATITIS.—Jaundice developing during or following the course of therapy for other disease or after immunization procedures of various types has been noted in the medical literature for nearly a century. In 1885 an epidemic of this type was reported in Germany in persons vaccinated for smallpox, where glycerinated humanized lymph had been used. Medical experience in the United States and in Europe demonstrated the frequent occurrence of jaundice in patients treated with arsphenamine or in

diabetic clinics. Later there were large outbreaks of hepatitis in individuals immunized against yellow fever with a vaccine which contained human serum as a stabilizing agent (21, 22). Other reports recorded similar events after blood transfusions, plasma infusions and administration of convalescent serum. Thus it was established that there is in the blood of certain individuals an agent capable of producing hepatitis on parenteral inoculation into recipients. The disease occurs not only in association with the injection of blood, blood products or vaccines to which serum has been added; in addition, it results from the use of incompletely or inadequately sterilized medical equipment, such as syringes, needles, lancets and scalpels.

In the utilization of blood from blood banks, serum hepatitis develops relatively rarely. The prevalence of carriers of virus among the blood donor population is probably less than 1 per cent, but to determine this with accuracy is difficult because many, if not most, patients to whom blood is administered receive more than a single unit and from numerous donors. The long incubation period of the disease further complicates the problem of adequate follow-up. Incidence following administration of human plasma varies with the quantity of plasma given and the size of the pools from which units were derived. It seems reasonable to suggest that the use of plasma should be restricted to disorders in which the need is absolute and that plasma given should be prepared from small pools. Other products derived from blood have come into common usage in the treatment of a variety of diseases. The usual method of preparation of protein fractions is by precipitation with ethyl alcohol in the cold. Gamma globulin and antihemophilic globulin fractions, prepared by this procedure, have apparently been free of icterogenic properties. Similarly, the albumin fraction after being heated to critical temperatures seems also to be safe. Topical thrombin, on the other hand, may carry the virus of serum hepatitis.

The population at risk to this infection is primarily one in which treatment for other disease processes is necessary. Therefore, serum hepatitis is more usually a disease of later life, in contrast to a peak incidence of infectious hepatitis in childhood and adolescence. Serum hepatitis may occur at any age, however. In younger individuals it is more likely to follow the use of vac-

cines of which human serum is a component, or the treatment of burns or injuries with blood or plasma. The two sexes are equally susceptible. The disease seems to be widely distributed geographically but is of highest incidence in areas where medical care is readily available and highly developed. By definition, serum hepatitis is transmitted by artificial means. How the virus is disseminated in the population under natural circumstances is not known. One possibility is that of placental transfer from a mother who is a carrier of the virus to her offspring in utero. Viremia also makes possible the transmission by insect carriers, but, as stated before, there is no evidence that spread occurs by this means.

There are special risks to infection among hospital personnel. Cases have been reported in physicians, surgeons, pathologists, nurses, laboratory technicians and assistants in blood banks (23). The occupational hazard results from the frequent handling of materials and equipment contaminated with the viral agent. Small abrasions of the skin produced by contaminated needles and scalpels afford an avenue of ingress for the virus, risks which may be avoided or controlled only by cautious handling of presumably infected equipment and strict adherence to procedures of asepsis. The recognition of carriers is difficult, since in most instances there have not been clinical manifestations of hepatitis and laboratory and serologic tests are not totally effective in designating individuals with viremia.

PATHOLOGY

The mortality rate from infectious hepatitis is relatively low and of the order of 0.1–0.2% in large groups of cases. In the past the few fatal cases which came to autopsy were described as acute or subacute yellow atrophy of the liver of undetermined origin and with little or no consideration of infection of viral origin. Moreover, there was no ready means of obtaining biopsy specimens of liver from nonfatal cases until the development of the procedure of punch biopsy by Roholm and Iverson in 1939 (24). With improved opportunities for the study of the disease, more adequate descriptions of morphologic and cellular changes were

recorded. Pathologic manifestations of infectious hepatitis and serum hepatitis are the same and are not differentiated in any way. Therefore, a single description will be given—it applies to viral hepatitis in both of its recognized clinical forms.

Much information concerning the pathology of the liver in viral hepatitis has been derived from the reports of Dible, McMichael and Sherlock (25), Lucké (26) and Mallory (27). In the early and acute stages of the disease there are evidences of inflammation in periportal areas and within hepatic lobules. In portal regions the predominant cell types are mononuclear, including lymphocytes, histiocytes and plasma cells. Neutrophils and eosinophils are also usually present. There is evidence of degeneration and necrosis of liver cells in widely distributed areas within the lobule, and focal necrosis is associated with acidophilic changes in the degenerating cells. There is also disruption of the usual radial arrangement of cords of liver cells so that the lobule is thrown into a state of disarray. Mitoses and multiple nuclei are seen early in the disease in liver cells and less frequently in bile duct epithelium, demonstrating that from the onset the liver attempts to respond by regenerating cells and replacing necrotic foci. If icterus has appeared, bile thrombi in biliary canaliculi and droplets of bile within the cytoplasm of cells in central areas of the lobule are likely to be seen. Nonicteric cases may have fewer histologic changes, and biliary thrombi are not observed. With recovery from the acute disease there is repair of the lesions within the liver, the evidences of inflammation persisting for perhaps the longest period. Ordinarily, there is no residual scarring or increase in quantity of fibrous connective tissue.

Deaths due to viral hepatitis fall into the categories of (*a*) fulminant hepatitis, with death within 10 days of onset, and (*b*) the subacute form, in which there is fatal termination after 10 days, usually from 3 to 8 weeks after onset, although it may be delayed to as late as 6 months. The fulminant process is one of acute massive necrosis of the liver. The organ is reduced little in size and weight, is soft, and the capsule is wrinkled. Microscopically, there is widespread necrosis, with autolysis of cells apparently beginning in central areas and extending to the periphery until

only narrow rims of morphologically intact hepatic cells remain at the outer margins of the lobules. Inflammatory reactions are consistently present in portal areas with accumulation of large numbers of mononuclear cells and with fewer neutrophils and eosinophils. Similar evidences of inflammation are found within the lobule, but the extent of the change in this area is variable. In some instances infiltrates occur at sites of dissolution of hepatic cells. Mitosis of liver cells and of bile duct epithelium are seen even in cases in which death has occurred within a few days of onset. The primary pathologic changes associated with fulminant hepatitis seem to be limited to the liver. Other findings may be explained as secondary to the rapid and massive necrotic process in this organ. Included are hemorrhagic manifestations in skin and gastrointestinal tract, splenomegaly, ascites, bile nephrosis and encephalopathy. Although most patients are deeply jaundiced at termination, fulminant hepatitis may in rare instances occur without associated icterus.

The pathology of subacute hepatic necrosis due to viral hepatitis includes all the changes observed in fulminant hepatitis but differs in that the initial process of necrosis is not so widespread, inflammatory changes are less, and the reaction of regeneration is greater. The liver in this instance is usually atrophic and of less than normal weight and size. Deep scars mark the surface in areas of earlier massive necrosis, while large nodular areas of regenerating liver are to be seen between fibrotic depressions. Mallory (27) is of the opinion that necrosis and degeneration of entire lobules makes regeneration impossible, and in these areas there is collapse of reticulum and fibrosis. In other lobules in which the necrotic process is limited to central areas, regeneration of liver cells proceeds from the normal cells at the periphery. Regenerating cells may be abnormally large and multinucleate, and lobular structure is not always totally reconstituted. Inflammatory changes are of the same type as in fulminant hepatitis but are quantitatively less. Peculiar to the subacute form is the development of obliterating endophlebitis involving efferent veins. The author observed the development of the Chiari syndrome in an adolescent girl who died from subacute hepatic necrosis apparently due to in-

fectious hepatitis. At autopsy there was widespread involvement of central vessels with thrombi of varying age (28).

Other forms of liver disease may develop as sequelae to viral hepatitis. These may become manifest after periods of months or many years following the attack of hepatitis. The most important is postnecrotic cirrhosis (29), but portal cirrhosis (30) and biliary cirrhosis (31) have also been observed. It has been claimed that biliary atresia in the newborn may evolve from viral hepatitis developing in utero (10).

CLINICAL MANIFESTATIONS AND COURSE OF ACUTE VIRAL HEPATITIS

The clinical manifestations of infectious hepatitis and serum hepatitis are similar. In the individual patient, differentiation can be achieved only when there is knowledge of the source and route of infection. However, some minor differences seem to exist in terms of the frequency with which certain symptoms and signs accompany the two processes in large groups of patients. Therefore, the clinical description, as recorded below, relates to both types of infection except where note is taken of possible dissimilarities.

EARLIEST SYMPTOMS AND SIGNS (PREICTERIC PERIOD).—The first manifestations of viral hepatitis are those of a constitutional or gastrointestinal disorder. Among the more commonly occurring symptoms are those of lassitude and fatigue, loss of appetite, nausea and vomiting. Often, there is fever at onset with temperatures varying from 100 to 103 F., although fever is less likely to occur in patients with serum hepatitis. Other symptoms include headache, myalgia and skin eruptions of an urticarial or morbilliform type. Within an interval of from one to a number of days the urine may be noted to be deeply colored and the stools acholic. At this time, also, pruritus often occurs. There may be abdominal pain or discomfort, usually most marked in the right upper quadrant or in the epigastrium. The frequency of occurrence of these symptoms in 200 young adults with viral hepatitis is recorded in Table 1. Physical examination may reveal little

other than slight elevation of temperature and discomfort or nausea when the abdomen is palpated. Usually there is pain when pressure is applied or a blow struck over the right lower thorax. Lymphadenopathy in cervical chains, particularly in the posterior cervical, may be noted.

In usual descriptions of the disease this earliest phase is re-

TABLE 1.—Frequency of Occurrence of Symptoms in the Preicteric Phase of Viral Hepatitis in 200 Patients*

Symptoms	No. of Cases	% of Cases
General symptoms:		
Lassitude and fatigue	137	68.5
Pruritus	93	46.5
Fever	83	41.5
Headache	53	26.5
Chills	34	17.0
Upper respiratory infection	31	15.5
Muscle and joint pains	24	12.0
Syncope	16	8.0
Epistaxis	9	4.5
Cough	8	4.0
Urticaria	6	3.0
Symptoms referable to disease of the liver or gastrointestinal tract:		
Anorexia	184	92.0
Urine dark	181	90.5
Nausea	158	79.0
Vomiting	117	58.5
Abdominal pain	114	57.0
Acholic stools	109	54.5
Constipation	45	22.5
Diarrhea	19	9.5
No preicteric symptoms	15	7.5

* From Hoagland, C. L., and Shank, R. E.: Infectious hepatitis: A review of 200 cases, J.A.M.A. 130:615, 1946.

ferred to as the preicteric period. It may be of variable length; and termination, by definition, is indicated when jaundice ensues. The average duration of the prodromal period is about five days. However, icterus appears as the first manifestation of hepatitis in 10–15% of patients, and in rare instances symptoms occur as long as two to three weeks in advance of demonstrable icterus. A prolonged preicteric period is much more likely in serum hepatitis than in infectious hepatitis.

In anicteric or subicteric forms of the disease, jaundice does not develop, making clinical recognition difficult. This apparently occurs frequently in younger children and is not an uncommon form of the disease in later life. Diagnosis and early institution of therapy of hepatitis without icterus is important because complications and sequelae may evolve, just as in the icteric form of the disease.

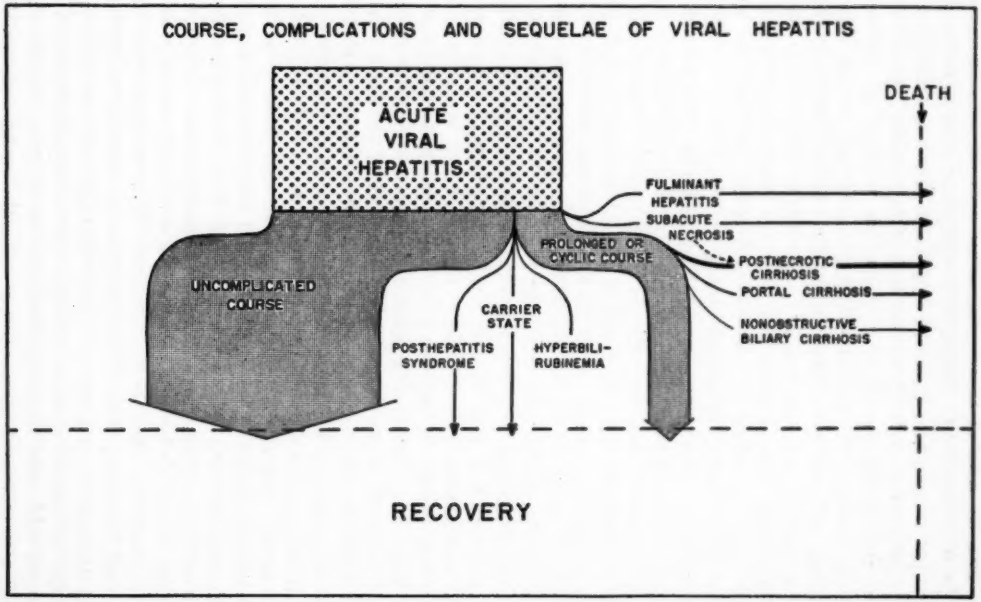
Laboratory tests of hepatic function may be particularly useful in establishing an early diagnosis. If the disease is suspicioned, certain tests should be undertaken. Of greatest assistance may be determinations of urine bilirubin and urobilinogen, serum bilirubin and bromsulfalein retention. Often bromsulfalein retention is increased before hyperbilirubinemia occurs. Similarly, the ratio of free to total cholesterol in serum is increased at an early date and frequently before the advent of jaundice. The thymol turbidity and cephalin-cholesterol flocculation reactions of serum may be elevated relatively early in the course of the disease. The white blood cell count, although often within normal limits, may be reduced to leucopenic levels during earliest phases of hepatitis.

Icteric period.—With the development of jaundice, previously occurring symptoms usually decrease in severity. Nausea and vomiting occur less commonly, but lassitude and asthenia persist as jaundice appears and deepens. Fever no longer is present in the uncomplicated disease. The urine is dark and the stools light in color. Pruritus may decrease as icterus becomes clinically discernible, but in many instances it persists as a bothersome complaint until jaundice recedes. Discomfort and pain in the upper abdomen are common symptoms. The peak of icterus may be reached within three or four days, but more usually not until the tenth to fourteenth day. At this time or shortly before, anorexia decreases and the appetite improves. Gradually, thereafter, there is return of strength and the feeling of well being. As food intake increases, there is restoration of the body weight lost earlier in the course of the disease.

During this period, icterus of the skin and sclerae is observed. The liver is palpable below the costal margin in most patients and is tender, but splenomegaly rarely occurs. In patients without demonstrable hepatomegaly, pain may be elicited by firm pres-

sure over the area of hepatic dullness. Spider angiomata appear in the occasional case. Bradycardia with pulse rates as low as 40 to 50 per minute may be noted in patients who are deeply jaundiced or most severely ill. Occurrence of hemorrhagic manifestations and ascites should be accepted as evidence of extensive hepatic damage. As convalescence proceeds and icterus slowly subsides, physical manifestations of the disease disappear. The icteric period varies in length but averages about 25–30 days. Under usual circumstances the liver no longer is palpable or tender after jaundice has disappeared and blood levels of bilirubin have returned to normal values.

PERIOD OF CONVALESCENCE.—Viral hepatitis is a relatively benign disease in most instances. As jaundice recedes and symptoms and signs ameliorate, the patient proceeds to complete recovery. However, the full return of normal physical strength and energy and the restoration of body weight may require several weeks. In young adults the loss of body weight during the acute course of the disease may vary from but a few pounds to as much as 25 or 30 pounds. It is important that sufficient time be allowed for recovery and that observation of the patient be continued until convalescence is complete. Recurrence of symptoms and signs may develop in patients permitted to return to usual activities at an early date, particularly if the expenditure of relatively large amounts of physical energy is entailed. If convalescence is interrupted by return of symptoms of anorexia, nausea or abdominal tenderness, or if icterus, hepatic tenderness or hepatomegaly recur, the patient should again be placed on a regimen of close observation and medical management. In the military services the average period of hospitalization and observation for patients with viral hepatitis is between 50 and 60 days. Although so long a period of hospitalization in civilian populations may be impractical or impossible because of costs, it is essential that each patient be as carefully observed and treated. The results of carefully selected laboratory tests of liver function are essential to the best evaluation of the progress and completeness of recovery. Although complications and sequelae develop in but a small proportion of patients with viral hepatitis, these may be of grave significance, leading to prolonged illness or even to death (see figure, page 18).


COURSE, COMPLICATIONS AND SEQUELAE OF VIRAL HEPATITIS
DEATH
ACUTE VIRAL HEPATITIS
FULMINANT HEPATITIS
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PROLONGED OR CYCLIC COURSE
POSTNECROTIC CIRRHOSIS
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UNCOMPLICATED COURSE
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COMPLICATIONS OF VIRAL HEPATITIS

A variety of complications may evolve during the course of viral hepatitis. These may be grouped in two categories. In one there is delay in convalescence, and recovery occurs only after months of slow but persistent restoration of hepatic function or with a cyclic course of recrudescence and remission; while in the other, complications lead directly and unrelentingly to a fatal issue, as in fulminant hepatitis and subacute necrosis.

PROLONGED COURSE.—If convalescence is not complete after four months, the course of the disease may be considered to be unduly prolonged. Most patients in whom such a delay in recovery has occurred will proceed to eventual complete restoration of hepatic function over additional periods of from 2 to 14 months. The frequency with which the course of the disease is thus prolonged undoubtedly varies, but it is influenced by many factors, including such characteristics of the patient as age and general health. Most extensive observations have derived from groups of military personnel, in which it has been noted that about 15–20% of all patients with viral hepatitis have a prolonged course (32, 33).

Manifestations are similar to those of the acute disease but are usually of gradually decreasing intensity. Certain patients will recover from icterus but will continue to have symptoms of fatigue, depressed appetite and hepatic tenderness. The liver may remain palpable, and in occasional instances spider angiomata may appear only to disappear at a later date. Although serum bilirubin concentrations may be normal or only slightly elevated, other tests of liver function remain abnormal. Bromsulfalein retention is usually increased, and thymol turbidity values may be markedly elevated for many weeks. Results of these tests gradually revert to normal values as recovery slowly proceeds.

In other instances, patients remain icteric for long periods and pruritis may even be increased in intensity. There is elevation in the alkaline phosphatase activity of serum and in total serum cholesterol, though other laboratory tests of hepatic damage show little abnormality. The clinical picture becomes one of obstructive jaundice, and differentiation from other lesions causing biliary

obstruction and requiring surgical intervention may be difficult. This syndrome has been called "cholangiolitic hepatitis" (34). It may not be desirable to preserve this terminology, however, since cholangiolar lesions are difficult and sometimes impossible to demonstrate in biopsy specimens of liver. Certain patients who exhibit this form of prolonged hepatitis fail to recover totally, and cirrhosis of the biliary type evolves.

CYCLIC COURSE.—Recrudescence of hepatitis may occur after partial or complete recovery from an initial attack. The relapse may be associated with a return or increase in severity of symptoms, but in many instances is noted only by means of laboratory tests. Although exacerbations of the disease may occur at any time during the first six months after onset, they are most likely to develop as the patient is permitted to increase his activity during convalescence. In occasional cases there are multiple phases of remission and recrudescence. The relative severity of the initial attack seems to bear no relationship to the likelihood of relapse. Although repeated acute attacks of the disease lengthen the course, most patients go on to eventual complete restoration of hepatic function. If a second attack of hepatitis occurs six or more months after recovery from the first, it is reasonable to assume that there may have been a second infection, probably by a virus different from that first involved.

FULMINANT HEPATITIS.—Deaths directly due to viral hepatitis are infrequent. The case fatality rate in large epidemics of infectious hepatitis and serum hepatitis is of the order of 0.1–0.2% of clinically recognizable forms of the disease (2, 3, 22, 26). Since it is well established that subclinical infections without jaundice do occur, the actual rate is undoubtedly lower. Deaths due to serum hepatitis in previously hospitalized patients occur more frequently and are contributed to by the more advanced age of patients and the presence of other disease processes (35). A form of hepatitis causing death in as many as 50% of women in the postmenopausal period in the Scandinavian countries has been described (18). A malignant course of the disease may be contributed to by the older age of the patient, debility, coexistence of other disease, pregnancy and delay in obtaining medical treatment of the acute process. The author observed a patient

who was a long distance runner and whose only symptom prior to participating in a race on a hot summer day was tiredness. He collapsed after the race, proceeded to develop rapidly progressive signs of hepatic failure and died of the disease after 10 days (36). In another case, a woman pediatrician who, while pregnant, had attended several children with hepatitis died only five days after delivery and the appearance of the first manifestations of hepatitis. It is probable that there are variations in virulence of the virus and that the size of the inoculum producing infection and the extent of exposure influences the severity of infection. The relative mildness or severity of early manifestations are of little or no assistance in determining which cases may go on to most severe course, since fatalities occur in patients with few initial symptoms and without icterus. Therefore, it is of particular importance that infection be recognized early and treatment instituted.

If the course of the disease is short and death occurs within 10 days of onset, the process is recognized as *fulminant hepatitis* (26). In such patients there is rapid development of evidences of massive hepatic damage with vomiting and inability to retain foods taken by mouth, fever, hemorrhagic manifestations, ascites and edema, and rapidly deepening stupor progressing into coma. Muscular twitching and convulsions occasionally occur. Jaundice is usually present, but in rare instances death intervenes before icterus has become clinically apparent. The entire course of the disease may involve no more than 2 days, but more usually it requires 4–10 days. Laboratory tests afford evidence of marked retention of bromsulfalein, even when serum bilirubin values are only slightly increased. The concentration of total serum cholesterol decreases, and values less than 75 mg./100 ml. are not unusual. Prothrombin time is markedly increased, but the thymol turbidity and cephalin-cholesterol flocculation reactions may be only slightly abnormal. Leukocytosis with values from 12,000 to 25,000 are usually recorded.

Once the fulminant course of hepatitis has been established, there is rapid and dramatic progression of deterioration. It is of the utmost importance to observe the patient frequently and to attempt to treat new abnormalities, such as anemia, electrolyte

imbalance and hypoglycemia, as they become manifest. Unfortunately, therapy usually accomplishes little more than temporarily retarding the rapid progress of this malignant form of hepatitis.

FATALITIES WITH SUBACUTE COURSE.—Deaths due to viral hepatitis may occur after a somewhat more prolonged or subacute course. In most such instances, fatal termination comes in 3–12 weeks after onset. The earlier course of the disease may have differed in no notable fashion from that of the usual case of viral hepatitis. More frequently, however, the early phases of the disease have been marked by relatively severe manifestations. In other cases there is delay or interruption of recovery, as in prolonged or relapsing hepatitis. Eventually, the occurrence of restlessness, incoherence, delirium or stupor or the development of purpura or ascites marks the onset of hepatic failure. The patient may then proceed into hepatic coma and finally to exitus. In still other instances there may be a remittent course with evidences of improvement which are only temporarily maintained. Clinical manifestations terminally are similar to those of fulminant hepatitis.

SEQUELAE

Following attacks of viral hepatitis, certain patients fail to recover totally and may be left with residual defects. Among the sequelae to be considered are persistent hyperbilirubinemia, post-hepatitis syndrome, the carrier state and chronic forms of liver disease leading to the evolution of cirrhosis.

PERSISTENT HYPERBILIRUBINEMIA.—In most large groups of patients who have had viral hepatitis and have recovered completely, in so far as clinical and laboratory observations permit this deduction, a few have been found to have a single but persistent abnormality in bile pigment metabolism. This results in sustained elevation of serum bilirubin concentration, with greater increase in the indirect, as compared to the direct, reacting bilirubin. Although the degree of hyperbilirubinemia may fluctuate from time to time, there are no attendant symptoms of disease. The author has observed several such patients over a number of

years. In none of these has the quantity of the pigment in the blood reverted to normal values, and fluctuations have usually occurred within the range of 1.0–3.0 mg./100 ml. It is tempting to conclude that an attack of viral hepatitis may induce a permanent defect in the handling of bile pigments by hepatic cells, thereby accounting for hyperbilirubinemia. This remains a hypothesis, however; and Neefe suggests that some, if not all, of these cases may be explained on the basis of pre-existing constitutional or familial hyperbilirubinemia (11). Nevertheless, the defect is apparently without significance in terms of later development of chronic forms of liver disease, and the only discomfort which it is likely to cause the patient is one of appearance, since the skin and sclerae may become jaundiced when blood levels of bilirubin are highest.

POSTHEPATITIS SYNDROME.—Occasional patients have persistent complaints of abdominal discomfort, anorexia, intolerance to fatty foods and fatigue following recovery from acute attacks of hepatitis and in the absence of clinical and laboratory evidence of hepatic dysfunction. Such patients may find it impossible to return to previous duties and activities for many weeks or months, and even relatively minor expenditures of physical energy may lead to complaints of marked fatigue and exhaustion. A variety of studies have failed to demonstrate defects in intermediary metabolism which would account for the symptoms. It seems likely that psychosomatic factors contribute in a major way. However, it is advisable that the problem be approached cautiously; and if symptoms persist, a punch biopsy specimen of liver should be obtained and examined to add to other laboratory evidence indicating normal function and morphology.

CARRIER STATE.—Virus may be present in blood or feces long after recovery from infectious hepatitis or serum hepatitis (37, 38). Carriers of the IH virus may disseminate the disease through contaminated feces and possibly through blood, whereas the risk from carriers of SH virus seems to be due solely to presence of the virus in blood. How frequently the carrier state occurs is not known, and it is unlikely that this information will become available until methods have been evolved for transmitting infection to an experimental animal or for propagating and identifying the

virus by means other than by transmission to volunteers. Certain individuals who are suspected of being carriers give a history of prior illness like that of hepatitis or have laboratory evidence of liver damage. Many, however, have not been jaundiced or ill, and tests of liver function demonstrate no abnormality.

CHRONIC TYPES OF LIVER DISEASE.—A few patients who have had prolonged or cyclic courses of viral hepatitis fail to recover completely, and evidences of hepatic damage and dysfunction persist. Eventually there are evidences of chronic liver disease and the clinical picture becomes that of cirrhosis of the liver with manifestations such as palmar erythema, spider angiomata, gynecomastia, distention of venous collaterals in the abdominal wall, hepatomegaly, splenomegaly, esophageal varices, ascites and edema. Death from cirrhosis may result within a year of the attack of viral hepatitis or may be delayed for a much longer period. The most common pathologic type is postnecrotic cirrhosis. In other instances the lesion cannot be differentiated from portal cirrhosis, and rarely is the pathology that of biliary cirrhosis (Fig. 1).

The possibility remains that other patients who apparently recover totally from an acute attack of viral hepatitis continue to have a smoldering but slowly progressive process in the liver which leads eventually to cirrhosis. In addition, it is possible that subclinical and undiagnosed viral hepatitis may lead eventually to cirrhosis. Proof of such eventualities has not been established, however. The information available from study of groups of military personnel indicates that less than 1% of patients who have had icteric forms of the disease later develop cirrhosis. Under any circumstances, the risk of developing cirrhosis following hepatitis must be small and perhaps little or no greater than in the population at large (39). However, it is important to note the relationship and to consider viral hepatitis among the etiologic factors of cirrhosis.

DIAGNOSIS OF VIRAL HEPATITIS AND EVALUATION OF LIVER FUNCTION

Recognition of the disease in its various manifestations and stages depends on thoughtful evaluation of clinical observations

and selection of laboratory procedures permitting appraisal of liver function. Once icterus is apparent in a young individual with characteristic symptoms and laboratory findings of liver damage, there is usually little difficulty in making the diagnosis, although it should be recognized that even in this instance the diagnosis is presumptive and arrived at by exclusion, since specific procedures are not available for isolating or determining the presence of the hepatitis viruses. It may be necessary to consider and exclude other acute disorders producing hepatic damage, such as infectious mononucleosis, Weil's disease, amebic hepatitis and exposure to hepatotoxins. Jaundice without other evidence of depression in liver function may result from constitutional hyperbilirubinemia, hemolytic anemia and obstructive lesions in the biliary tract. It is of particular importance that careful consideration be given in differential diagnosis to lesions producing extrahepatic biliary obstruction, since surgical relief of obstruction may be required and should be achieved before long standing obstruction has produced liver damage. Of equal importance, however, is the necessity for avoiding surgical procedure, whenever possible in patients with viral hepatitis, since these patients tolerate surgery poorly. Therefore, if there is uncertainty in diagnosis, it is preferable to delay exploratory laparotomy until additional observations have been made.

Because the liver participates in many metabolic processes, a great variety of laboratory determinations can be utilized as tests of liver function. The information made available by proper selection and use of these tests is of great value in achieving a diagnosis and in following the course of viral hepatitis. However, it should be recognized that the evidence provided is of qualitative rather than quantitative value and that the degree of abnormality in the results of one test need not, and often does not, parallel that for another type of determination. Space will not permit complete discussion of tests of liver function and their application for diagnostic and other study of patients with viral hepatitis. However, consideration will be given to determinations of value in the various stages of the disease.

Clinical recognition of viral hepatitis during preicteric periods or without icterus may indeed be difficult. The patient may pre-

sent himself with symptoms characteristic of an acute infection or of an acute gastrointestinal disorder. If hepatic tenderness or hepatomegaly is demonstrable, the diagnosis of hepatitis should be considered. However, these physical abnormalities are often not present early in the disease. It should be remembered that a history of previously occurring viral hepatitis does not exclude a second attack, since at least two different viral agents may produce the disease. Although a history of injections of blood products or of contact may be a useful lead to the diagnosis, more usually this information is not elicited, except during epidemic periods. Early in the course of the disease it is important to examine the urine daily for evidences of bile or to determine urinary urobilinogen and serum bilirubin, since these values may exceed normal prior to clinical detection of icterus of the sclerae or skin. The initial increase in serum bilirubin is primarily in the prompt reacting fraction. The cephalin-cholesterol flocculation and thymol turbidity reactions often are positive before the onset of icterus and are usually so in anicteric hepatitis. Bromsulfalein retention is increased and frequently becomes an important objective measure of the course of the subicteric or anicteric disease. In a similar manner, the ratio of free to total cholesterol may be increased.

Once icterus has become apparent, the chief problem in diagnosis is in the differentiation of extrahepatic and hepatocellular causes. The history and physical findings often contribute salient considerations, but laboratory tests of hepatic function assist greatly in making this differentiation. If the increase in total serum bilirubin is accompanied by relatively little rise in alkaline phosphatase activity of serum, i.e., values of from 6 to 10 Bodansky units, it is likely that the disorder involves hepatic parenchymal damage, since a greater increase in serum alkaline phosphatase is likely to occur in extrahepatic obstructive lesions of the biliary tract. Similarly, in the latter conditions the total serum cholesterol is often increased substantially; whereas in the usual course of viral hepatitis, total cholesterol concentrations in serum remain unchanged or only slightly elevated and there is a relatively great increase in the ratio of free to total cholesterol. Strongly positive cephalin-cholesterol flocculation or thymol tur-

bidity reactions in patients with jaundice of recent development afford evidence of liver damage. Tests of bromsulfalein retention provide little useful information for purposes of differential diagnosis in deeply jaundiced patients. However, determination of markedly enhanced retention of the dye when levels of serum bilirubin are less than 4.0 mg./100 ml. may be indicative of an intrahepatic lesion. Under ordinary circumstances, changes in concentration of serum albumin and in prothrombin activity do not occur in viral hepatitis unless the disease is prolonged or especially severe. Other determinations, such as galactose tolerance or hippuric acid synthesis, may be used to determine hepatic function; but the results of these tests usually only confirm and add relatively little to the results of other procedures more commonly used.

It is desirable to have available certain procedures which permit assessment of liver function as the patient proceeds into convalescence or into other phases of the disease. Particularly useful in this regard is bromsulfalein retention when serum bilirubin levels approach normal values. Thymol turbidity, zinc turbidity and cephalin-cholesterol flocculation reactions usually reach peak values shortly after maximum levels of serum bilirubin are recorded. They then begin to recede, frequently not returning fully to normal until bromsulfalein retention is no longer increased. A secondary rise in the results of the turbidity or flocculation tests may give early evidence of a relapse.

It is desirable to utilize punch biopsy procedures to obtain specimens of liver for morphologic examination whenever additional information is needed for purposes of diagnosis. However, it should be recognized that the procedure is not wholly without risk and, therefore, should be used advisedly and avoided whenever there are manifestations of hemorrhage or when prothrombin time is prolonged.

TREATMENT

Specific therapeutic agents are not available for treating viral hepatitis. However, two general principles of management guide therapy: rest and restriction of activity, and provision of food that is adequate in content of protein and calories (40).

It is advisable to place all patients at bed rest during early and active phases of the disease. This is best accomplished in the hospital. Although the earlier procedure was to maintain bed rest until all symptoms and physical manifestations had disappeared and results of laboratory tests of liver function approached normal values, recent observations in groups of military personnel have demonstrated that patients may safely be permitted to be out of bed with freedom about a hospital ward after acute symptoms have subsided (41). The potential advantages of relaxation of strict adherence to a regimen of total bed rest are several. Moving about may add to the comfort of the patient and enhance appetite. Moreover, it may shorten the period of adaptation to physical activity during convalescence. Nevertheless, it is of utmost importance that rest in bed be instituted early in the disease and be maintained until acute manifestations have largely subsided. The physician must be guided by the condition of his patient, and it will be necessary to continue bed rest for longer periods for patients who are more severely ill, who are in older age groups, who are pregnant or who have other diseases. Jaundice and evidence of moderate liver damage, if symptoms have largely abated, should not mediate against lessening restrictions of activity. In mild cases, strict adherence to a regimen of bed rest may not be needed for periods longer than five days to a week. On the other hand, the persistence of symptoms of nausea, vomiting, fever or abdominal pain and of laboratory evidence of severe liver damage may warrant continuance of bed rest for a much longer period. It is advisable to release restrictions gradually, permitting the patient to be out of bed only for an hour or two the first day and then daily increasing freedom of activity about the room or hospital ward until the patient is allowed to be up and about freely, except for 1 or 1½ hour periods after meals throughout the remainder of the period of hospitalization. In addition, there should be 9 to 10 hours of sleep at night.

Dietary factors have an integral role in protection against, and in repair of, experimental liver damage in animals. Similarly, such factors are important in therapy of diseases of the liver in man. In the treatment of viral hepatitis, provision is made for a highly nutritious diet, relatively high in calorie, protein and vita-

min content. For a young adult of average body size the diet planned may afford approximately 3,000 calories and contain about 375 Gm. carbohydrate, 150 Gm. protein and 100 Gm. fat. The caloric content may be less for an older or a smaller person and may contain about 2,500 calories and 100 Gm. protein. Fat should be maintained at moderate levels of intake, since it affords extra calories and adds to the palatability of the diet (42). There is no evidence that dietary fat is harmful. However, fried foods may not be easily digested and should, therefore, be avoided. Although it has been reported that very high levels of protein intake may be harmful and lead to symptoms of stupor or precoma in patients with advanced liver disease (43), generous provision of protein in the diet of patients with viral hepatitis is strongly indicated. It is the author's belief that only in patients with severe liver disease with deviation of portal blood flow is there likelihood of difficulty arising from protein feeding. A well planned diet will afford quite adequate intake of most of the vitamins; and there is, therefore, usually no important purpose to be achieved by provision of vitamin supplements.

Early in the course of the disease anorexia, nausea and vomiting may make it manifestly impossible to achieve the desired levels of dietary intake. If vomiting is severe, it is necessary to provide glucose, water-soluble vitamins and fluids by intravenous injections. Ordinarily, little is gained by using an intranasal polyethylene tube, but this procedure may be very helpful in treating patients in the precomatose or comatose states associated with fulminant hepatitis. Appetite is sometimes stimulated by intramuscular injections of crude liver extract or vitamin B_{12}. Early in the disease, it is advantageous to afford quantities of easily digested soft or liquid foods which the patient desires and will eat, and then daily to encourage consumption of larger quantities and greater variety of food. Alcoholic beverages should be avoided totally, not only during treatment of the acute disease but for a period of six months after convalescence is complete. There is no evidence that dietary supplements of lipotropic agents, such as methionine, choline, or inositol, are of therapeutic value in hepatitis. It should be pointed out, however, that reports indicate that fatty infiltration of the liver has resulted in certain

patients maintained on high calorie diets for relatively long periods (44). It is advisable, therefore, to modify the diet, reducing caloric intake as the patient regains the body weight lost during the acute phase and as liver function returns to normal.

Careful consideration should be given to the choice of drugs utilized in attempting to afford relief from distressing symptoms. In occasional instances dramamine may reduce nausea and anorexia. Pruritus often is a very bothersome complaint. Although few procedures afford significant relief, starch baths or benadryl are sometimes of value. If sleeplessness or agitation of the patient makes necessary the use of sedatives, selection should be carefully made because of the enhanced action of many of these compounds in patients with moderate or severe liver damage. It is desirable to avoid the use of narcotics and barbiturates. Paraldehyde or benadryl would seem to be somewhat more safely used.

A number of recent papers establish a claim for the use of cortisone in the treatment of viral hepatitis (45, 46). Effects of the hormone are apparently those of stimulating appetite, increasing the rate at which hyperbilirubinemia is reduced and permitting earlier return of normal hepatic function. There is evidence, however, that relapse and recrudescence occur more frequently in patients treated with cortisone. At this time, therefore, it would seem to be premature to accept the addition of cortisone to the procedures utilized in the routine treatment of viral hepatitis. If used, patients should be followed especially carefully so that manifestations of relapse may be recognized early.

The active period of therapy is concluded when the patient is free of symptoms, hepatomegaly and hepatic tenderness have disappeared and laboratory tests of liver function approach normal. At this time the total serum bilirubin should be less than 1.5 mg./100 ml., and bromsulfalein retention less than 8% at 45 minutes. Usually the thymol turbidity and cephalin flocculation tests will have reverted to negative or only weakly positive reactions. The patient then may be permitted increasing activity outside the hospital or home. Liver function tests should be repeated and the patient examined after a further interval of two to three weeks. If he continues to be asymptomatic and no evidences of relapse are apparent in tests of liver function, he may

be permitted to return to work or usual activities. However, the patient should be alerted to return to the physician at once if there is recurrence of symptoms. In addition, plans should be made for follow-up examination and appraisal on several occasions in the succeeding six month period.

If the course of the disease is prolonged or relapses occur, treatment like that of the acute disease should be administered. In most severe forms of the disease, treatment must be heroic, with every effort made to sustain life and to afford opportunity for repair and regeneration of the profoundly damaged liver. Treatment for chronic forms of the disease become those adapted for cirrhosis of the liver.

PREVENTION

Precautions must be taken in the hospital and home for control of the disease and its transmission. Since in most instances it cannot be definitively stated that a single case is due either to IH or SH virus, it is advisable that all patients be placed in intestinal isolation. How long such isolation should be maintained cannot be answered with authority. It is likely that in many cases of infectious hepatitis the virus does not persist in the stool for periods longer than several weeks. In others, however, contamination of feces undoubtedly persists for many weeks or even months. Therefore, for greatest safety it is desirable to maintain intestinal isolation for most, if not all, of the period of hospitalization.

Dissemination of virus by equipment contaminated with blood or by the use of blood products must be carefully controlled. All syringes, needles and lancets used in hospital or office practice should be used in but a single patient and then sterilized by autoclaving or boiling, since other methods of decontamination cannot be depended upon. Blood plasma should never be used indiscriminately, and only then if prepared from relatively small pools. Since a significant proportion of blood donors have a history of viral hepatitis or have abnormalities in tests of liver function, it is advisable to establish a procedure in blood banks or blood donor stations which would avoid the use of blood from such donors. Zinc turbidity and thymol turbidity reactions may be

readily determined on aliquots of blood, and those units discarded in which these reactions are positive. Similarly, all donors with a past history of viral hepatitis probably should be excluded. Although this procedure will not totally avoid the risk of transmission of viral hepatitis through the therapeutic use of blood or blood products, it should substantially reduce it.

Specific passive prophylaxis for infectious hepatitis is afforded by intramuscular injection of 0.01 ml. concentrated human gamma globulin per pound of body weight. Since the type of infection is seldom absolutely established, gamma globulin should be used even though it is suspected that the contact has been with infection due to SH virus. It is especially important to use prophylaxis when there has been recent intimate exposure by individuals who have other diseases or are pregnant or debilitated.

SUMMARY

During the past 15 years many important contributions to the knowledge of viral hepatitis have been made. However, the incidence of the disease in its two forms—infectious hepatitis and serum hepatitis—remains high. The currently available information has here been reviewed and evaluated in an effort to demonstrate how the physician may utilize the modern knowledge of viral hepatitis in approaching problems of diagnosis, treatment and control.

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